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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/607,903 | 06/27/2003 | Gjalt W. Huisman | MBX 025 DIV CON | 7536 |

23579 7590 02/01/2010

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| EXAMINER | |
|---|---|
| HUTSON, RICHARD G | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 02/01/2010 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/607,903 | HUISMAN ET AL. | |
| | Examiner | Art Unit | |
| | Richard G. Hutson | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,6-8,11,12,14-16,19 and 21* is/are pending in the application.

4a) Of the above claim(s) *11,12,14-16,19 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/10/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/10/2009 has been entered.

Claims 1-4, 6-8, 11-12, 14-16, 19 and 21 are still at issue and are present for examination.

Applicants' arguments filed on 12/10/2009, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 11, 12, 14-16, 19 and 21 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Liebl et al. (J. Bacteriology 174(6): 1854-1861 (1992)).

This rejection was stated in the previous office action as it applied to previous claims 1, 2, 4, 6 and 8. In response to this rejection applicants have not amended the claims, but rather filed a declaration by Professor Wolfgang Liebl and traverse the rejection as it applies to the claims in light of the filed declaration.

It is acknowledged that the original rejection which was stated in the office action of 3/10/2006, and has been maintained and altered as a result of applicants amendment of the claims and previous arguments.

Applicants continue to traverse this rejection on the basis that applicants submit that Liebl does not recite all of the claim limitations and does not enable one of ordinary skill in the art to make the claimed bacteria.

Applicants continue to argue this rejection on the same basis as previous and submit that the Examiner alleged that Liebl discloses the claimed bacterial strain from *E. coli,* at Table 1, in which Liebl teaches the propagation of ASO19/PWNuc5 in *E coil* and C. *glutamicum*. Office Action mailed March 12, 2009. Applicants submit that this referred to teaching is not tantamount to a disclosure of *E. coli,* genetically modified to *express* a heterologous nuclease gene, wherein the nuclease gene product is *secreted* into the periplasmic space and released when the bacteria is lysed. Applicants submit that the *E. coil* was simply used as a host for plasmid propagation and applicants submit that a careful review of the disclosure in Liebl et al. does not indicate any data with

respect to expression and secretion of SNase in *E. coli*. Applicants submit that the claims require that the bacterial strains express the heterologous nuclease gene, and secrete it into the periplasmic space and there is no such disclosure in Liebl with respect to *E. coli*.

Applicants support this position by drawing the Examiner's attention to the enclosed declaration under 37 C.F.R. § 1.132, executed by Prof. Wolfgang Liebl, the lead author of the Liebl reference, which notes that no expression of the SNase enzyme is described in the Liebl reference with respect to E. *coli*. ("Liebl declaration") See especially, item 7 of the Liebl declaration. Thus, applicants submit that the Examiner's allegation that Liebl discloses clearly teaches the *E. coli* which expresses and secretes a nuclease into the periplasmic space is incorrect.

Applicant's complete argument and the declaration by Prof. Wolfgang Liebl are acknowledged and have been carefully considered, however, are not found persuasive in overcoming the current rejection for the reasons previously presented and repeated herein.

Applicants are again reminded that applicant's claims are directed to a bacterial strain and not a method of using such a claimed bacterial strain. With this in mind, applicants attention is directed to applicants claims which recite the claimed bacteria cell is an E. coli bacterial cell which is genetically modified to express a heterologous nuclease gene, which Liebl et al. clearly teach as discussed above and in Table I and the supporting text.

Applicants argue that the E.coli cells taught by Liebl et al. which are genetically modified to express a heterologous nuclease gene, do not express and secrete the encoded SNase enzyme. The declaration of Professor Liebl is acknowledged in its support of this assertion.

In spite of applicants argument and the submitted declaration that the heterologous gene is under control of an inducible promoter, "the nuclease gene product is secreted into the periplasmic space and released when the bacteria is lysed." This characterization of the taught bacterial strain is based upon the fact that "the nuclease gene product" of the "heterologous nuclease gene" whether it be a polypeptide or a nucleic acid, is secreted into the periplasmic space and released when the bacteria is lysed. This characterization of the cell which expresses a heterologous gene product is further supported by the fact that the "nuclease gene product" which is a polypeptide also comprises an appropriate signal peptide.

Additionally as previously stated, applicants claim 1 recites that those bacteria that express this heterologous nuclease must do so such that the nuclease gene product is secreted into the periplasmic space and released when the bacteria is lysed. As stated in response to applicant's previous response, it is clearly the case that when the bacteria are lysed, the nuclease gene product what ever it is, is secreted into the periplasmic space and released. Applicants continue to not address this basis of the maintenance of the rejection.

Thus claims 1, 2, 4, 6 and 8 remain anticipated by Liebl et al.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 and 6-8, are rejected under 35 U.S.C. 103(a) as being unpatentable over Greer et al. (WO 94/10289 (1994)), Atkinson et al. (Biochemical Engineering and Biotechnology Handbook 2nd edition, Stockton Press: New York, 1991) and Lee et al. (Production of poly(hydroxyalkanoic Bacteriology, 174(6): 1854-1861 (1992)) or Miller et al. (J. Bacteriology, 169(8): 3508-3514 (1987)).acid, Adv. Biochem. Eng. Biotechnol. 52:27-58, 1995), in view of Liebl et al. (J. Bacteriology, 174(6): 1854-1861 (1992)) or Miller et al. (J. Bacteriology, 169(8): 3508-3514 (1987)).

This rejection was stated in the previous office action as it applied to previous claims 1-4 and 6-8. In response to this rejection applicants have not amended the claims, but rather filed a declaration by Professor Wolfgang Liebl and traverse the rejection as it applies to the claims in light of the filed declaration.

Applicants again review the legal standard, and then review applicant's interpretation of what each of the references teaches. After this analysis, applicants submit that "A combination of Greer, Liebl, Miller, Atkinson and Lee does not recite all of the elements of the claims". In response to this argument applicants are again reminded that this rejection is based upon the obviousness of the claims in light of the

teachings of the prior art references and that it is unnecessary for the combination of Greer, Liebl, Miller, Atkinson and Lee to recite all of the elements of the claims, in order for the claims to render obvious the rejected claims.

Further, applicants are again reminded that applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants again submit that Liebl and Miller disclose genetically engineering the gram positive bacteria *C. glutamicum* and *B. subtilis* respectively, to secreted nuclease into the culture medium and as noted above in response to the 102 (b) rejection, this is not tantamount to a disclosure of secretion of nuclease into the periplasmic space as claimed. In response to this argument, as is pointed out above, Liebl et al. additionally teach the genetically engineered *E. coli* .

Applicants submit that the claimed bacterial strains are engineered to (1) produce large amounts of nuclease which is (2) secreted into the periplasm where it is harmless to the cell, until release by cell lysis and that none of Greer, Atkinson or Lee makes up for these deficiencies, as Greer is not concerned with genetically engineering bacterial strains to secrete nuclease, Lee discloses the production of copolyesters in *Pseudomonas sp* and Atkinson is a review of biochemical and biotechnological methods and reagents. Applicants submit that the availability of biotechnology tools does not make obvious results obtained from their use. With respect to claim 7, none of the prior

art discloses genetically modifying bacteria with the heterologous nuclease gene integrated into the chromosome, and the gene product secreted into the periplasmic space.

As above, each of applicants points are acknowledged, however, not found persuasive for the reasons of record, the reasons discussed above and for those repeated herein. Applicants are again reminded that the instant rejection is based upon obviousness as a result of the combination of the references and not anticipation and that thus it is not necessary that the references teach the specific points applicants argue.

Applicants submit that there is no motivation to combine the references as the Examiner has done and even such a combination does not arrive at the claims. In response to this argument, as previously stated,

One of ordinary skill in the art would have been motivated to genetically engineer a bacterial strain to express the *Staphylococcal aureus* nuclease as taught by Liebl et al. or Miller et al. or a homologous nuclease gene that has been modified to enhance nuclease activity, so that this bacterial strain would produce and excrete the nuclease into the bacterial growth medium as part of a fermentation process for the synthesis of industrially important molecules. Applicants are reminded that Liebl et al. teach such in C. glutamicum and also in E. coli. A nuclease excreted into the medium as a result of such a genetically engineered bacterial strain would a inherently result in the degradation of at least 95% of all the nucleic acid released following lysis of the cells in

less than 24 hours. The motivation for producing a nuclease by a genetically engineered bacterial strain used in the fermentation process is to reduce the amount of nucleic acids in the medium which result in an increase in the viscosity of the medium, causing problems in the downstream processing steps, as taught by Greer et al. Greer et al. give further motivation for genetically engineering a bacterial strain to express a nuclease, because they teach that purified preparations of nucleases are expensive and a bacterial strain that was genetically engineered to express a nuclease activity would not require an external nuclease or hydrogen peroxide to be added to the fermentation. One would have had a reasonable expectation of success because both Liebl et al. and Miller et al. were able to express functional *Staphylococcal aureus* nuclease in different bacterial species, including *Corynebacterium glutamicum*, *Bacillus subtilis* and E. coli and Liebl et al. teach that the *Staphylococcal aureus* nuclease is a heat-stable biochemically well characterized enzyme. One would have been further motivated to engineer the bacterial strain to secrete the nuclease into the growth medium in an effective amount to enhance the recovery of product from the growth medium. Alternatively one would have been motivated to engineer a homologous nuclease to increase its nuclease activity for the same reasons as stated above for the introduction of the heterologous *Staphylococcal* nuclease.

Further, one would have been motivated to optimize the above fermentation conditions as taught by Lee et al. in order to more efficiently produce the desired product, consisting of antibiotics, organic acids, amino acids, proteins, vitamins, polyhydroxyalkanoates and polysaccharides as taught by Atkinson et al. Optimization

of fermentation conditions includes the choice of the bacterial host such as *Methylobacterium organophilum*, *Methylobacterium extorquens*, *Alcaligenes eutrophus*, *Alcaligenes latus*, *Azotobacter vinelandii*, *Pseudomonas oleovorans*, *Pseudomonas resinovorans*, *Pseudomonas acidovorans* and *Escherichia coli* or any other microorganism which produces the desired product as taught by Atkinson et al. or Lee et al. For example, Atkinson et al. teach that Alcaligenes eutrophus has been studied in detail due to its ability to accumulate large amounts of P(3HB) (i.e. ability to grow to cell densities of approximately 85 g/l and produce P(3HB) at 61.5 g/l, or 80% wt/wt of dry cell mass, page 30 through 32). It would have been obvious to use a bacterial strain which grows to a high cell density and/or which produces a high level of the desired product.

Applicants continue to point out that applicants claims are directed to a bacterial strain that are engineered to (1) produce large amounts of nuclease which is (2) secreted into the periplasm where it is harmless to the cell, until release by cell lysis, continues to be acknowledged as previously and above, however, this is still not considered entirely accurate. Applicants are reminded that applicants claim 1 is directed to a bacterial strain for the production of polyhydroxyalkanoates, wherein the bacterial strain is selected from a group including *E. coli* and is genetically modified to express a heterologous nuclease gene, wherein the nuclease gene product is secreted into the periplasmic space and released when the bacteria is lysed. It is noted that this claim is still considered to be anticipated above by Liebl et al., as upon lysis of the

bacterial strain taught by Liebl et al. the nuclease gene product is secreted into the periplasmic space and released.

Applicants continued argument on the basis of evidence of secondary considerations including commercial success, long felt but unresolved needs, failure of others and unexpected results, etc. is acknowledged, however, is not found persuasive for the following reasons. First it is unclear as to what if any specific "evidence of secondary considerations" applicants are referring to in their presented argument, as applicants submitted argument regarding microbial fermentations for the use of manufactured products, and needs and motivations associated with such are not considered evidence of these of secondary considerations or if they are it is unclear as to what applicants stated points evidence. Further, applicant's submission of applicant's discovery is not considered a secondary consideration, nor is the motivation that the skilled artisan would want to ultimately integrate the nuclease into the chromosome considered a secondary consideration.

Thus it continues that these secondary considerations are further acknowledged but not found persuasive given the discussion previously and above.

Thus, claims 1-4 and 6-8, remain obvious in light of Greer et al. (WO 94/10289 (1994)), Atkinson et al. (Biochemical Engineering and Biotechnology Handbook 2nd edition, Stockton Press: New York, 1991) and Lee et al. (Production of poly(hydroxyalkanoic Bacteriology, 174(6): 1854-1861 (1992)) or Miller et al. (J. Bacteriology, 169(8): 3508-3514 (1987)).acid, Adv. Biochem. Eng. Biotechnol. 52:27-58,

1995), in view of Liebl et al. (J. Bacteriology, 174(6): 1854-1861 (1992)) or Miller et al. (J. Bacteriology, 169(8): 3508-3514 (1987)).

***Conclusion***

This is a continuation of applicant's earlier Application No. 10/607,903. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rgh
1/28/2010

/Richard G Hutson/
Primary Examiner, Art Unit 1652